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ASSOCIATION BETWEEN SEX HORMONES AND AMBULATORY BLOOD PRESSURE:

Sex hormones & ambulatory blood pressure

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Abstract

Introduction: Higher levels of total testosterone (TT) and lower levels of sex hormone binding globulin (SHBG) have been associated with increased blood pressure (BP) in women with an inverse association between TT and BP among men. Fewer studies have examined associations with 24-hr ambulatory blood pressure (ABP), blunted nocturnal BP decline or the role of dehydroepiandrosterone sulfate (DHEAS), a precursor to androgens.

Methods: Baseline blood samples were assayed for 229 normotensive men (≥50 years) and women (≥55 years) participating in the VITamin D and OmegA-3 TriaL. Standardized seated BP (systolic [SBP] and diastolic [DBP]) and 24-hr ABP were measured by trained technicians. Self-reported cardiovascular risk factors and sociodemographic variables were reported on baseline questionnaires. Sex stratified linear regression models adjusted for age, race/ethnicity, body mass index, smoking and alcohol estimated the association between each sex hormone and measures of BP and 24-hr ABP. Logistic regression used to estimate associations with blunted nocturnal decline (>10% reduction in SBP or DBP during sleeping hours).

Results: TT and SHBG demonstrated significant inverse correlations with SBP while DHEAS was not significantly associated with BP. Among men, in multivariable analyses, each 10% increase in DHEAS was associated with a 0.41 mmHg higher seated DBP (β=4.29, 95%CI: 0.84, 7.73) and each 10% increase in TT and SHBG was associated with a 0.54 mmHg (β=−5.65, 95%CI:−10.45,−0.84) and 0.60 mmHg (β=−6.30, 95%CI: −11.38,−1.21) decrease in seated DBP, respectively. No significant associations were observed among women.

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Conclusions: Among men only, we observed statistically significant inverse cross-sectional associations between TT and SHBG with seated DBP, and a significant positive association with DHEAS levels.

Keywords

sex hormones; ambulatory blood pressure; blood pressure; sex hormone binding globulin; testosterone; dehydroepiandrosterone sulfate

Introduction

Hypertension is the most common major modifiable risk factor for cardiovascular and kidney disease in the US and worldwide. The prevalence of hypertension (a systolic blood pressure [SBP] ≥140 mmHg and/or a diastolic blood pressure [DBP] ≥90mmHg) is nearly 29% among US adults.[1] However, the prevalence is differentially distributed by age and sex. Among those aged <60 years the prevalence is higher among men (18–39 years: 8.4%, 40–59 years: 34.6%) compared to similarly aged women (18–39 years: 6.1%, 40–59 years: 29.9%). However, after age 60 years the prevalence among women (66.5%) surpasses that of men (63.1%).[1] In 3,344 middle-aged adults (mean 52.6 ± 14.5 years), Hermida et al.[2] demonstrated that women exhibited an equivalent elevated risk of cardiovascular events at lower wake and sleep SBP than men (awake SBP: women=124 mmHg, men=135 mmHg; asleep SBP: women=109 mmHg, men=120 mmHg; $P_{\text{interaction}}$<0.009), with a steeper increase in SBP-related cardiovascular risk among women compared to men. Together these data suggest a role for sex hormones in hypertension etiology.

In observational studies, higher levels of total testosterone (TT) and sex hormone binding globulin (SHBG) have been associated with lower BP and a lower incidence of hypertension.[3–8] Dehydroepiandrosterone sulfate (DHEAS), a precursor to nearly half of androgens in adult men and all androgens in postmenopausal women,[9] has infrequently been assessed for its association with either BP[4, 10] or 24-hr ambulatory BP (ABP).[11] It is unclear whether DHEAS is associated with BP independently or through conversion to other androgens.[9] Clinic-measured seated BP measurements may exhibit high within-person variability, which may lead to attenuated associations. Research among diverse populations of older and elderly adults has demonstrated 24-hr ABP predicts future cardiovascular endpoints more strongly than clinic based BP[12] and may vary by sex.[13] Additionally, 24-hr ABP decreases measurement error and increases statistical power allowing for the detection of modest associations and improves the ability to examine differences in nocturnal BP decline. Importantly, previous studies have not examined these associations exclusively among normotensive individuals, in whom more subtle associations may be present as a precursor to hypertension development.

Blunted nocturnal BP decline, defined as a <10% decline in nocturnal BP (both SBP and DBP), has been significantly associated with a greater risk of all-cause mortality, total cardiovascular disease, cardiovascular mortality and target organ damage in hypertensive patients.[14] However, few studies have examined the role of a blunted nocturnal decline among normotensive individuals. Hermida et al.[15] reported that blunted nocturnal decline

was significantly associated with a greater multivariable risk of total CVD events irrespective of hypertension status (normotensive: HR=1.71; hypertensive: HR=2.46). However, it is unclear whether blunted nocturnal decline varies by sex, as data have been conflicting[16–19] along with a lack of multivariable analyses. Therefore, to understand the potential influence on measures of blood pressure among normotensive adults, we examined whether concentrations of DHEAS, TT and SHBG were associated with seated BP, 24-hr ABP and blunted nocturnal decline among a racially diverse population of men and women.

Materials and Methods

Study Population: VITamin D and OmegA-3 TriaL (VITAL)

We utilized data from the **VIT**amin D and Omeg**A**-3 Tria**L** (VITAL), for which details of the trial design have been previously published.[20] In brief, VITAL is an ongoing randomized, 2×2 factorial design primary prevention trial of 25,874 ethnically diverse men (≥50 years) and women (≥55 years), testing 2,000 IU/day cholecalciferol, 1 g/day marine omega-3 fatty acids (Omacor® fish oil, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) fatty acids, both agents, or both placebos, with an expected mean follow-up of 5 years for cardiovascular and cancer endpoints. Between 2011 and 2014, participants free of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, transient ischemic attack or coronary revascularization were randomized. All participants completed extensive baseline self-administered questionnaires to obtain data on age, race/ethnicity, relevant cardiovascular risk factors, dietary, lifestyle and behavioral factors, and socio-demographic covariates.[20]

A subcohort of 401 VITAL participants without hypertension at baseline (SBP <140 mmHg, DBP <90 mmHg, no self-reported prior diagnosis of hypertension or history of anti-hypertensive treatment) from 12 major metropolitan areas completed in-home examinations by trained and standardized personnel from Examination Management Services, Inc. (EMSI). Participants provided blood and urine, with anthropometrics, standard seated and 24-hr ABP measured. Analyses were limited to the 229 participants (106 men and 123 women) with 24-hr ABP measures available.

Baseline blood collection

Participants of the EMSI subcohort were instructed to fast for their morning in-home visit. Blood samples were collected in sodium heparin tubes which were processed immediately. Blood samples were assayed for DHEAS, TT and SHBG concentrations by paramagnetic particle chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA) at Harvard Catalyst Clinical Research Center (Boston, MA). All intra-assay coefficients of variation were less than 10% (DHEAS: 1.6–8.3%, TT: 1.7–3.9% and SHBG: 4.5–4.8%) and all Inter-assay coefficients of variation were less than 11% (DHEAS: 3.7–11.3%, TT: 4.2–7.1%, SHBG: 5.2–5.5%).

Standardized Blood Pressure and 24-hr Ambulatory Blood Pressure (ABP) Assessment

At the baseline EMSI in-home visit, participants provided standardized measurements of seated BP and 24-hr ABP. Two separate standardized seated BP readings taken at least 30

seconds apart were collected using a mercury sphygmomanometer after the participant had sat for 5 minutes before blood draw, or >30 minutes after blood draw using standardized procedures.[21] ABP over 24 hours was measured using the SPACELABS 90207 device, usually worn on the belt or pant/skirt-line connected to the upper arm by cord. Both systolic and diastolic BP were recorded every 20 mins during the day and every 60 mins at night. Actual sleeping hours were available for 73% (n=168) of participants; therefore, primary analyses utilized *a priori* set sleeping hours set from 10 pm to 6 am. However, sensitivity analyses among those with at least one sleep and wake time were conducted. At the end of the in-home EMSI visit, staff individually fit and affixed the device on participants, provided instructions and manually initiated 2–3 readings to familiarize the participant. After the 24-hr monitoring period, participants returned the instrument to EMSI in a provided pre-paid overnight mailer. The raw data were downloaded from each instrument by EMSI technicians using SPACELABS 92506 Report Management System (PC-compatible Interface) and regularly transferred the data to VITAL study staff.

The SPACELABS 90207 has been extensively validated in multiple populations [22–27] and has been used successfully in numerous studies of participants of various ages and underlying co-morbidities.[12, 28–39] Moreover, the SPACELABS 90207 fulfills both the British Hypertension Society and Association for the Advancement of Medical Instrumentation criteria for mean differences versus a mercury sphygmomanometer of <5 mmHg for both SBP and DBP with a standard deviation of <8 mmHg.[26]

Statistical Analysis

Distributions of baseline characteristics were compared across sex and extreme quartiles of sex hormones (DHEAS, TT and SHBG). All calculations of 24-hour ambulatory BP were conducted using the raw data as collected. Partial Pearson correlations for each sex hormone and BP measure (seated SBP and DBP and 24-hour ambulatory SBP and DBP) were adjusted for age (in years) and sex. Additionally, descriptive statistics for all BP measures were calculated across extreme quartiles of each sex hormone and stratified by sex and age. Multivariable linear regression models estimated the association between each sex hormone and mean seated BP and 24-hr ABP, separately. Each sex hormone was continuously modeled after log transformation to achieve normality. Estimates can be interpreted as the unit change in each respective measure of BP for a 10% increase in each respective sex hormone.[40] Blunted nocturnal decline was defined as a <10% reduction in 24-hour ambulatory SBP (aSBP) or DBP (aDBP) during sleeping hours, defined *a prior* as 10 pm to 6 am.[41] Multivariable logistic regression models estimated the association between each sex hormone and blunted nocturnal decline, presented as odds ratios (OR) and corresponding 95% confidence intervals (95% CI). All models were stratified by sex, and adjusted for potential confounders and hypertension risk factors in two nested models. Model 1 adjusted for age and race, while model 2 additionally adjusted for BMI (kg/m^2), smoking status, and alcohol consumption. In sensitivity analyses, we excluded women actively using hormone therapy medication (n=9) and expanded model 2 to additionally adjust for multivitamin use and fruit and vegetable intake. Additionally, among participants with actual sleep and wake times, sensitivity analyses were conducted to utilize these data in lieu of *a priori* defined times. Multivariable models (model 2) for associations between each

sex hormone and BP measure were adjusted for duration of sleep while blunted nocturnal decline was redefined based on actual sleep and wake times. All p-values were two-sided. Analyses were conducted with SAS (version 9.2; SAS Institute, Cary, NC).

Statement of Ethics

This study was approved by the Institutional Review Board of Brigham and Women's Hospital and all procedures followed were in accordance with institutional guidelines. Participants provided written informed consent to participate.

Results

In this population of normotensive men and women, the mean seated SBP (122 ± 13 mmHg and 120 ± 12 mmHg, respectively) and aSBP (130 ± 12 mmHg and 128 ± 11 mmHg, respectively) did not vary by sex ($p>0.05$). However, seated DBP and aDBP did vary by sex, with values higher among men than women (mean seated DBP: men=73 ± 10, women=70 ± 10 mmHg, $p=0.02$; aDBP: men=79 ± 7, women=76 ± 8 mmHg, $p<0.01$). Moreover, 40% of men and 48% of women were classified as exhibiting blunted nocturnal SBP decline ($p=0.26$), while 30% of men and 20% of women were classified with blunted nocturnal DBP decline ($p=0.09$). Baseline factors varied significantly by sex and quartiles of sex hormones (Table 1). Among men and women, those in the highest versus lowest quartile of DHEAS were younger, while those in the highest quartiles of SHBG were older compared to the lowest quartile. BMI varied inversely and significantly across extreme quartiles of SHBG and TT, with a lower BMI observed among those in the highest versus lowest quartile of SHBG in men and women, and in the highest versus lowest quartile of TT among men, but not women. TT concentrations varied significantly across extreme quartiles of SHBG among men; however, among women, TT and SHBG levels varied significantly only across categories of DHEAS.

All sex hormones were significantly correlated with one another in age and sex-adjusted Spearman correlations (Table 2). DHEAS was significantly and positively correlated with TT ($r=0.30$; $p<0.0001$) and inversely correlated with SHBG ($r=-0.19$; $p<0.01$), while TT and SHBG were significantly and positively correlated ($r=0.26$; $p<0.0001$). When examining correlations between sex hormones and continuous BP measures (seated SBP, seated DBP, aSBP, aDBP), DHEAS was not significantly associated with any BP measure. TT ($r=-0.15$, $p=0.02$) and SHBG ($r=-0.21$, $p<0.01$) each had a significant, moderate inverse correlation with seated SBP. Similar correlations were observed between SHBG and seated DBP ($r=-0.15$, $p=0.03$) and aSBP ($r=-0.14$, $p=0.03$). Additional adjustment for BMI attenuated the observed correlations between SHBG and BP toward the null, and all but the association between SHBG and seated SBP ($r=-0.14$, $p=0.04$) were no longer statistically significant. Variation of BP measures across age, sex and extreme quartiles are presented in Table 3. Among older men, seated SBP and aSBP were significantly lower among men in the highest versus lowest quartile of TT ($p<0.05$). There were no other consistent findings for measures of BP and blunted nocturnal decline across strata of age, sex and sex hormones.

In analyses adjusted for age and race among men, each 10% increase in DHEAS was associated with a significant 0.43 mmHg increase in seated DBP ($\beta=4.48$, 95% CI: 1.16,

7.81); the estimate was materially unchanged by multivariable adjustment for covariates in model 2 (β=4.29, 95% CI: 0.84, 7.73; Table 4). In contrast, TT and SHBG both demonstrated significant inverse associations with seated and 24-hour ABP in men. Notably, in the fully adjusted model 2, each 10% increase in TT was associated with a 0.54 mmHg decrease in seated DBP (TT: β=−5.65, 95% CI: −10.45, −0.84) and with similar results observed for SHBG (β=−6.30, 95% CI: −11.38, −1.21). The change in point estimates between model 1 and model 2 were largely due to the additional adjustment of BMI and alcohol consumption. In sensitivity analyses, additional adjustment in model 2 for multivitamin and fruit and vegetable intake did not materially change the estimates (results not shown). There were no statistically significant findings observed among women across any measure of BP, irrespective of whether women on hormone therapy were included or excluded from the analysis. In sensitivity analyses among participants with actual sleep and wake times, estimates for each multivariable model 2 adjusted for actual sleep duration were materially unchanged, except for the association between TT and mean seated SBP. Specifically, among men, after adjustment for duration of sleep, a statistically significant association was observed between TT and mean seated SBP (β=−8.32, 95% CI: −15.22, −1.42), which was in contrast to the estimates observed in model 2 (β=−5.14, 95% CI: −10.92, 0.63) but similar to results obtained from model 1 (β=−7.77, 95% CI: −13.30, −2.24; Table 4).

We did not find evidence of a statistically significant multivariable association between sex hormones and blunted nocturnal decline in SBP measured by 24-hour ABP. Among men only, TT was significantly associated with a greater odds of blunted nocturnal decline in DBP (OR=4.68, 95% CI: 1.11, 19.73) after adjusting for covariates in model 2. However, given the wide confidence interval the estimate should be interpreted with caution. Overall, higher levels of DHEAS were suggestive of a non-significant lower odds of blunted nocturnal SBP decline among both men (OR=0.76, 95% CI: 0.36,1.63) and women (OR=0.79, 95% CI: 0.43,1.44), and of blunted nocturnal DBP decline among women (OR=0.63, 95% CI: 0.30,1.32) when adjusted for covariates in model 2. In contrast, higher levels of SHBG were associated with a non-significant greater odds of blunted nocturnal SBP and DBP decline among both men (SBP: OR=1.60 95% CI: 0.51, 5.03; DBP: OR=3.63, 95% CI: 0.90,14.67) and women (SBP: OR=1.19, 95% CI:0.55, 2.57; DBP: OR=1.56, 95% CI: 0.58,4.17). Among women, estimates were materially unchanged when we excluded those currently using hormone therapy (results not shown). In sensitivity analyses among participants with actual sleep and wake times, estimates for blunted nocturnal decline were unstable due to the smaller sample size after the exclusion of participants without actual sleep and wake times. For example, null estimates remained null but demonstrated variability in the point estimates due to wide confidence intervals. The only estimate which changed dramatically was that for the association between TT and blunted nocturnal DBP decline, for which results were no longer statistically significant when restricted to those with actual sleep and wake times (OR=0.63, 95% CI: 0.17, 2.38) compared to the statistically significant positive association observed in model 2 (OR=4.68, 95% CI: 1.11, 19.73). However, it is important to note that in sensitivity analyses among those with actual sleep wake times, a greater number were classified with blunted nocturnal decline when

utilizing actual sleep wake times (men: blunted nocturnal decline based on actual sleep/wake times, n=52 vs blunted nocturnal decline based on a priori cut-off in full sample, n=32).

Discussion

In this cross-sectional analysis of middle aged normotensive men and women, we observed a significant association between DHEAS, TT and SHBG and seated BP only among men. Higher levels of DHEAS were significantly associated with higher seated DBP, while higher levels of TT and SHBG were significantly associated with lower seated DBP. We did not observe a significant association between sex hormones and measures of seated or ambulatory BP among women, irrespective of hormone therapy use. Furthermore, elevated TT was significantly associated with blunted nocturnal decline.

A key contribution of these analyses was the ability to examine 24-hr ABP and blunted nocturnal decline. To our knowledge, only one other study has examined these measures of BP in relation to DHEAS.[11] In contrast to our null findings, Barna et al.[11] reported that blunted nocturnal BP decline was associated with lower levels of DHEAS in a population of middle aged adults; however, only unadjusted analyses were presented. Given the paucity of available data, further work is needed to understand the role of sex hormones on blood pressure variability.

Few studies have examined the association between sex hormones and seated BP using multivariable analyses. Due to the strong relationship between sex hormones and other key demographic and chronic disease risk factors, we focus our discussion on those studies that have conducted multivariable analyses. The reported associations between sex hormones and seated BP vary substantially across individual hormones and by sex. For example, among men, the reported associations between TT, SHBG and seated BP have been consistent among the studies available. Male participants in a population-based study of Swedish adults aged 30–74 years, exhibited significant inverse associations between TT and SHBG with SBP and DBP (SBP: TT [β= −0.123, $p<0.001$], SHBG [β= −0.093, p=0.001]; DBP: TT[β= −0.097, p=0.001], SHBG[β= −0.113, $p<0.001$]).[7] Similar results for SBP were observed in a population-based study of Chinese men aged 20–89 years (TT: β= −0.02, 95% CI: −0.04, −0.01, SHBG:β= −0.14, 95% CI: −0.19, −0.09).[8] Although our findings for SBP were not statistically significant, they indicated a potential inverse association with TT and SHBG. Importantly, our population was restricted to normotensive individuals, which may partially explain the inconsistencies observed for SBP in our findings compared to previous reports which have typically included hypertensive participants with a wider range of BP.

In contrast to the associations between TT, SHBG and seated BP observed among men, findings for women have been mixed. In our population of postmenopausal women, we did not observe a significant association between DHEAS, TT or SHBG with any measure of seated BP. However, higher levels of TT have been significantly associated with higher SBP and DBP among postmenopausal, but not premenopausal, German women (SBP: β=7.11, $p<0.05$; DBP: β=3., $p<0.05$).[5] In longitudinal analyses including 5 years of follow-up in the same population, higher TT levels were significantly associated with higher SBP (β=3.46, $p<0.05$) but not DBP. SHBG has not been significantly associated with either SBP

or DBP.[5] In contrast, among postmenopausal female participants of the Beaver Dam Eye Study, higher SHBG levels were significantly associated with lower DBP (β=−2.31, p<0.001) independent of TT, while no association was observed with TT independently of SHBG, after adjustment for age, BMI and alcohol consumption.[3] Hence, given the few studies available, inclusion of hypertensives and mixed results, the underlying associations remain unclear.

Our findings for DHEAS and seated BP conflict with several studies which have reported positive associations with SBP and null associations with DBP.[3, 10, 42] Among a population based study of German adults aged 52–65 years, DHEAS exhibited a positive statistically significant association with SBP (β=3.18, p=0.04) but not DBP (β=0.85, p>0.05).[10] Similarly, two separate studies among women reported significant positive associations between DHEAS and SBP with mixed results for DBP,[3, 42] while another reported null findings for both.[43] These discrepancies may also be partially explained by variations in participant hypertension status across studies. DHEAS and its non-sulfated counterpart DHEA have been associated with hypertensive status;[4] therefore, it is possible that the positive associations observed in previous reports may be driven by BP values outside of the normotensive range.

Androgens have shown complex effects on BP in animal models through genomic and nongenomic pathways, further evidenced by the presence of androgen receptors on nearly all tissue types.[44] However, while animal models have suggested that elevated androgens increase BP and risk of hypertension, results from observational human studies often contradict these findings with lower levels associated with increased risk.[45] These discrepancies may reflect the key contribution of age; animal models are more often based on very young animals whereas observational studies in humans primarily focus on middle aged to older adults.[46] Androgens may exert influence on BP regulation by stimulation of sodium reabsorption, the increased synthesis of angiotensinogen in the kidneys as well as increased arterial pressure.[44] Moreover, significant associations between DHEAS and aldosterone have been previously reported, which may suggest that activity of the sympathetic nervous system may be influenced by associated changes in both.[47]

Several strengths and limitations, warrant further consideration. Important strengths include the ample sample size and seated standardized BP measured by trained staff. While the ample sample size allowed for stratified analyses by sex, we were still underpowered to examine variation by race/ethnicity, which has been shown to be associated with both sex hormone concentrations and BP measurements. Additionally, since this study was driven by the paucity of data with respect to DHEAS (a precursor to androgens) and measures of BP, we focused on TT and SHBG, which binds TT; however, further work to understand the role of estrogens is needed. Moreover, the cross-sectional nature of the design, hindered establishing the temporal sequence. However, it is important to consider that DHEAS, TT and SHBG have been shown to be relatively stable over time in both men and women; therefore, a single measure may reflect long term sex hormones levels.[48–51] Moreover, all exams were conducted in the morning, which reduced potential measurement error due to diurnal variation in TT.[52] Unfortunately, we were not able to estimate free testosterone, the bioavailable form of testosterone, due to a lack of albumin levels. Although, these

analyses were restricted to baseline BP measures, which may not fully capture changes in BP over time, 24-hr ABP measurements did allow for assessing changes in BP over the course of awake and sleeping hours. It should be noted that actual sleep hours were not available for all participants and primary analyses defined *a priori* sleep and wake times from 10 pm to 6 am; however, sensitivity analyses among the 73% of participants with actual sleep and wake times were materially unchanged from those utilized in the primary analyses. It should be noted that the use of actual sleep and wake times did result in a larger proportion of individuals identified with blunted nocturnal decline compared to those identified based on a priori sleep and wake times; however, the overall findings were not materially altered. Despite these limitations, these findings suggest minimal, bias due to the use of the *a priori* set sleep and wake times in the primary analyses.

Summary

In this cross-sectional study of normotensive adults, we found a potential inverse association for TT and SHBG, and a positive association for DHEAS, with seated DBP in men. However, no association was observed with seated SBP, 24-hr ABP or blunted nocturnal decline. Moreover, we did not observe an association between DHEAS, TT, and SHBG and BP among women. Given the paucity of available data, further work is needed to understand the role of sex hormones on blood pressure variability.

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Table 1.

Baseline characteristics of 229 normotensive adults by sex and extreme quartiles (Q1, Q4) of sex hormones

	Men (n=106)						Women (n=123)					
	DHEAS		Testosterone		SHBG		DHEAS		Testosterone		SHBG	
Characteristics	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
Demographics												
Age (years)	**66 ± 5**	**59 ± 5**	63 ± 8	64 ± 6	61 ± 7	64 ± 7	**66 ± 7**	**63 ± 5**	64 ± 7	65 ± 6	64 ± 6	65 ± 6
Black, %	33	50	42	23	**50**	**15**	34	52	57	56	47	48
Sex Hormones												
DHEAS (μg/dL) *	62 ± 23	282 ± 86	149 ± 113	123 ± 47	160 ± 101	146 ± 104	35 ± 12	170 ± 44	**57 ± 37**	**120 ± 69**	**106 ± 55**	**69 ± 39**
Testosterone (ng/dL) *	570 ± 254	563 ± 238	313 ± 78	931 ± 155	**388 ± 128**	**845 ± 231**	**21 ± 11**	**35 ± 14**	14 ± 2	51 ± 29	28 ± 12	29 ± 15
SHBG (nmol/L) *	54 ± 18	48 ± 19	**37 ± 14**	**73 ± 17**	28 ± 5	80 ± 12	**90 ± 37**	**61 ± 29**	79 ± 39	77 ± 37	35 ± 8	129 ± 26
Behavioral/Lifestyle risk factors												
BMI (kg/m^2)	30 ± 7	29 ± 5	**31 ± 7**	**25 ± 3**	**30 ± 5**	**25 ± 3**	27 ± 6	27 ± 5	28 ± 7	28 ± 7	**31 ± 8**	**25 ± 5**
Current smoking	7	12	8	8	8	12	10	6	7	9	17	10
Hormone therapy	-	-	-	-	-	-	3	6	4	9	7	10
Alcohol use †, %	70	80	69	73	73	69	55	61	64	52	48	61
Fruit/vegetables ‡	3.2 ± 2.3	3.2 ± 3.1	2.8 ± 1.8	3.9 ± 2.5	2.6 ± 1.7	3.8 ± 2.4	3.8 ± 2.6	3.7 ± 2.9	3.7 ± 2.5	3.4 ± 2.8	3.4 ± 2.5	4.9 ± 3.4

DHEAS: dehydroepiandrosterone; TT: total testosterone, SHBG: sex hormone binding globulin

Descriptive statistics for continuous variables are mean ± SD or median (min-max) and relative frequencies for categorical variables.

Bolded values indicated significant differences across extreme quartiles, based on t-test or Chi-square tests as appropriate ($p<0.05$)

* Geometric mean;

† >1 serving/week;

‡ Servings/day

Table 2.

Age and sex adjusted Spearman correlations * between sex hormones and blood pressure measures

	DHEAS	p-value	TT	p-value	SHBG	p-value
DHEAS	-	-	**0.30**	**<.0001**	**−0.19**	**<0.01**
Total Testosterone	-	-	-	-	**0.26**	**<.0001**
Seated SBP (mmHg)	0.003	0.96	**−0.15**	**0.02**	**−0.21**	**<0.01**
Seated DBP (mmHg)	0.09	0.18	−0.07	0.27	**−0.15**	**0.03**
Ambulatory SBP (mmHg)	0.03	0.64	−0.10	0.12	**−0.14**	**0.03**
Ambulatory DBP (mmHg)	0.002	0.97	−0.03	0.66	0.01	0.84

DHEAS: dehydroepiandrosterone; TT: total testosterone, SHBG: sex hormone binding globulin

* Adjusted for age and sex

Table 3.

Blood pressure measurements by extreme quartiles of sex hormones stratified by age and sex

		DHEAS		TT		SHBG	
		Q1	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
Men, <60	n=24	1	13	7	4	11	5
Mean Seated BP	Systolic	119 ± 0	119 ± 8	123 ± 5	113 ± 10	**123 ± 8**	**111 ± 11**
	Diastolic	81 ± 0	77 ± 7	79 ± 3	74 ± 10	75 ± 9	72 ± 8
Mean ABP	Systolic	134 ± 0	127 ± 7	126 ± 8	131 ± 4	127 ± 7	130 ± 4
	Diastolic	79 ± 0	81 ± 6	79 ± 6	82 ± 2	80 ± 5	81 ± 5
Blunted Nocturnal Fall, %	Systolic	100	31	29	50	36	60
	Diastolic	100	23	0	50	9	40
Men, >=60	n=82	26	13	19	22	15	21
Mean Seated BP	Systolic	125 ±17	125 ± 15	**129 ± 13**	**117 ± 13**	126 ± 11	120 ± 16
	Diastolic	**69 ± 12**	**78 ± 7**	71 ± 14	69 + 8	75 ± 9	72 ± 8
Mean ABP	Systolic	131 ± 10	134 ± 18	**135 ± 12**	**123 ± 8**	133 ± 8	126 ± 15
	Diastolic	77 ± 5	78 + 9	79 ± 4	76 ± 5	79 ± 5	78± 7
Blunted Nocturnal Fall, %	Systolic	46	46	42	50	53	48
	Diastolic	35	23	21	32	40	33
Women, <60	n=34	5	9	8	8	8	7
Mean Seated BP	Systolic	114 ± 9	121 ± 13	123 ± 12	120 ± 12	119 ± 18	118 ± 11
	Diastolic	72 ± 6	69 ± 13	68 ± 12	68 ± 13	70 ± 12	77 ± 8
Mean ABP	Systolic	118 ± 5	127 ± 11	129 ± 12	128 ± 9	128 ± 12	123 ± 9
	Diastolic	74 ± 3	80 ± 9	78 ± 5	77 ± 10	79 ± 9	77 ± 7
Blunted Nocturnal Fall, %	Systolic	60	56	38	63	**63**	**0**
	Diastolic	20	11	13	38	50	0
Women, >= 60	n=89	24	22	20	24	22	24
Mean Seated BP	Systolic	121 ±10	121 ± 13	121 ± 11	122 ± 12	**124 ± 10**	**116 ± 11**
	Diastolic	70 ±10	69 ± 9	70 ± 10	68 ± 10	71 ± 11	68 ± 10
Mean ABP	Systolic	129 ± 12	128 ± 11	129 ± 13	128 ± 8	128 ± 9	129 ± 11
	Diastolic	76 ± 7	76 ± 8	76 ± 9	75 ± 8	74 ± 6	76 ± 8
Blunted Nocturnal Fall, %	Systolic	54	50	55	46	45	58
	Diastolic	25	9	25	13	14	21

DHEAS: dehydroepiandrosterone; TT: total testosterone, SHBG: sex hormone binding globulin

Significant differences across extreme quartiles **in bold**, based on t-test or χ^2 tests as appropriate ($p<0.05$)

Table 4.

Multivariable association between sex hormones* (DHEAS, TT and SHBG) and measures of blood pressure stratified by sex, β (95% CI)

	DHEAS*	TT*	SHBG*
Men			
Mean seated BP			
SBP			
Model 1	−1.90 (−6.43, 2.64)	**−7.77 (−13.30, −2.24)**	−6.09 (−12.57, 0.39)
Model 2	−0.80 (−5.01, 3.42)	−5.14 (−10.92, 0.63)	−3.39 (−9.58, 2.80)
DBP			
Model 1	**4.48 (1.16, 7.81)**	−3.03 (−7.33, 1.27)	**−5.37 (−10.24, −0.50)**
Model 2	**4.29 (0.84, 7.73)**	**−5.65 (−10.45, −0.84)**	**−6.30 (−11.38, −1.21)**
Mean ABP			
SBP			
Model 1	−0.06 (−4.25, 4.13)	**−6.91 (−12.01, −1.80)**	**−5.79 (−11.75, 0.17)**
Model 2	0.52 (−3.58, 4.62)	−4.65 (−10.28, 0.98)	−3.11 (−9.13, 2.91)
DBP			
Model 1	0.46 (−1.90, 2.82)	−1.17 (−4.14, 1.80)	−2.08 (−5.45, 1.31)
Model 2	0.34 (−2.03, 2.72)	−0.40 (−3.71, 2.91)	−1.17 (−4.67, 2.34)
Women			
Mean seated BP			
SBP			
Model 1	0.90 (−2.49, 4.28)	0.13 (−4.27, 4.52)	−3.61 (−7.66, 0.45)
Model 2	0.74 (−2.68, 4.16)	−0.35 (−4.80, 4.09)	−3.11 (−7.47, 1.25)
DBP			
Model 1	−0.19 (−3.24, 2.86)	−0.09 (−3.96, 3.79)	−1.26 (−4.95, 2.44)
Model 2	−0.22 (−3.31, 2.86)	−0.14 (−4.08, 3.80)	−1.66 (−5.62, 2.29)
Mean ABP			
SBP			
Model 1	0.59 (−2.37, 3.55)	−0.20 (−4.05, 3.64)	−0.86 (−4.45, 2.73)
Model 2	0.75 (−2.26, 3.75)	−0.09 (−4.01, 3.82)	−1.19 (−5.05, 2.67)
DBP			
Model 1	−0.32 (−2.62, 1.97)	−0.21 (−3.19, 2.77)	1.31 (−1.46, 4.09)
Model 2	−0.31 (−2.62, 2.01)	−0.06 (−3.08, 2.95)	0.33 (−2.65, 3.30)

*Log transformed dehydroepiandrosterone (DHEAS), total testosterone (TT), and sex hormone binding globulin (SHBG)

Dependent variables are the BP measures, β coefficients can be interpreted as the unit change in each measure of BP for a 10% increase in each respective sex hormone

Model 1: Age and race

Model 2: M1 + smoking status, alcohol consumption, BMI (kg/m^2)